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10/566,697	05/10/2006	Heng Wang	2008-282	9761

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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/566,697	WANG ET AL.	
	Examiner	Art Unit	
	TERESA WESSENDORF	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,8-10 and 13-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,8-10 and 13-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/10/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 2-4, 8-10 and 13-25 are pending and under examination in the application.

Withdrawn Objection/Rejection

In view of the amendments to the disclosure providing sequence identifier numbers for all the sequences in the specification, the objection to the specification is withdrawn. Also with the cancellation of claim 7, the objection is withdrawn. The rejection of the claims under 35 USC 112, second paragraph is withdrawn in view of amendments to the claims and applicants' arguments.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 2-4, 8-10 and 13-25 as amended and added, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

the application was filed, had possession of the claimed invention for reasons of record as reiterated below.

The specification fails to provide an adequate written description of the claimed method utilizing gene vaccine components of such scope particularly a library of random gene sequences. The specification describes a method of making a polyepitopic obtained from the single organism, Malaria falciparum. Other than this single embodied organism, no other organism has been shown to produce polyepitopic chimeric gene vaccines. The disclosure does not indicate that the single embodied organism can be applied to any type of organism. Neither does the disclosure disclose which nor how the different epitopes in the numerous epitopes of an organism can be derived to produce the polyepitopic chimeric gene vaccines. In vaccine formation there is the issue of where the combination of more epitopes create many possibilities thus, making it impractical to assemble or construct library as used as a vaccine. It is impractical to assemble and construct polyepitopic gene vaccines let alone a library because it is complicated, costly and requires much work. More importantly, how to effectively design polyepitope genes and overcome the variability of pathogens is required for the development of gene vaccines. (See for example, Li M. et al. Chin. Med. J. Engl.), 112 (8), 691-7, particularly

the paragraph bridging pages 691-670.) The life cycle of Plasmodium falciparum which causes malignant malaria severely affecting human health is complicated and comprises four stages comprising asexual reproduction and sexual reproduction in humans and sexual reproduction and sporogony in mosquitoes. In humans there are exoerythrocytic (liver) and erythrocytic stages, while gametocyte and sporozoite stages are in mosquitoes. Such complex biological traits cause Plasmodium falciparum to have highly variable response against the immunoprotection of the host and drugs. It is not apparent how the different length ranges for the numerous different organisms can be ascertain based only on the single species, Malaria, given that the same organism in different species e.g., humans are different. Furthermore, it is well-known in the art that underrepresentation or overrepresentation of these different size range may not produce the e.g., epitope essential for vaccine formation.

[It is suggested that applicants recite that the polyepitopic chimeric gene is obtained from Malaria falciparum].

Response to Arguments

Applicants state that in response to the Examiner's suggestion, applicants have added new claims addressed expressly to a method for use in constructing polyepitopic chimeric gene

libraries from Plasmodia falciparum, noting however that original claim 10 limits the antigen of interest to antigens of Plasmodia falciparum.

In reply, none of the independent claims recite for P. falciparum, albeit as stated by applicants, claim 10 recites said P. falciparum.

Applicants state that the claims are drawn to a method for preparing polyepitope chimeric gene vaccines, not to such a gene vaccine itself. Applicants state that it is just such difficulties that the presently claimed method is intended to overcome, and its success in doing so is an indicia of its patentability. As the Examiner acknowledges, it is particularly difficult to construct a library of polyepitope chimeric gene vaccines in the case of a difficult organism such as Plasmodia falciparum which grows through four separate life stages. Applicants' success in doing so, as evidenced by the examples in the applicants' disclosure, shows the strength of the presently claimed method. Applicants' method is of general application, and is not in any way restricted to epitopes of antigens produced by any specific organism, such as Plasmodia falciparum. The method is of broad application, and the epitopes employed to prepare polyepitope chimeric gene vaccines can be obtained from antigens related to other infectious diseases, as well as tumor

or autoimmune diseases (claim 8). Applicants' exemplification of their method using a particularly difficult organism is an unmistakable indication that they were in possession of the invention claimed at the time the present application was filed.

In reply, it is not controverted that perhaps the success in solving the problems has been achieved for malaria P. Falciparum. However, the disclosure has not correlated the single species to the numerous polyepitopic present in any organism or P. falciparum of different strains. There is no guidance or direction given in the specification that would lead one skilled in the art to the different epitopes in different antigens in any organism or antigens in any kind of tumors. It is not readily apparent from the general statements in the specification or applicants' arguments as to the experimental conditions being applicable for one as applicable for all. This art is too complex because of the numerous unforeseen factors/effects even for a single individual gene, let alone a library (i.e., collection of millions of genes). Attention is drawn to the newly submitted Cai reference (Vaccine). Cai shows at e.g., page 275 that the slightest change in one parameter, e.g., temperature, affect the method, even as applied to an already specific polypepitopic peptide as P. falciparum. How

much more for an enormous polyepitope contained in any or all kinds of antigenic epitope(s)?

Applicant, at the time of filing, is deemed to have not invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004).

One may not preempt an unduly large field by the expedient of making broad prophetic statements in the specification and claim unless the accuracy of such statements is sufficiently supported by well-established chemical principles or by sufficient number of examples.

A "written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula [or] chemical name of the claimed (genus) subject matter sufficient to distinguish it from other materials". University of California v. Eli Lilly and Col, 43 USPQ 2d 1398, 1405(1997), quoting Fiefs V. Revel, 25 USPQ 2d 1601m 16106 (Fed. Cir. 1993.

New Matter Rejection

Claims 2-4, 8-10 and 13-25 as amended and added, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New claims 15, 19-22, which recites for e.g., "predetermined antigen epitope" and "specific immunological type" and "measured by a single strand conformation polymorphism" are all not supported in the as-filed specification. MPEP 714.02 clearly states that applicants point out where in the specification the new claim limitations appear. In the absence of such, the original disclosure does not provide support for the newly added claim limitations supra.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 2-4, 8-10 and 13-25, as amended and added, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 13 recites the limitation in step e) "the diversity of the polyepitope chimeric genes in **the** polyepitope chimeric gene expression libraries" and step f) (ii) "the immunogenicity of the expression products." There is insufficient antecedent basis for these limitations in the claim.

2. Regarding claim 20, the phrase "type" renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "type"), thereby rendering the scope of the claim(s) unascertainable, especially in the absence of positive support in the specification.

3. The term "predetermined" in claims 19-22 is a relative term which renders the claim indefinite. The term "predetermined" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be

reasonably apprised of the scope of the invention. It is unclear as to basis or standard by which the antigen epitope has been or can be predetermined, especially in the absence of positive support in the as-filed disclosure.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 102/103

Claims 2-3, 8-9 and 13-25, as amended and added, are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Chengtao, Lin et al (Chinese J. of Biochemistry and (Zhongguo Shengwu Huaxue Yu Fenzi Shengwu Xuebao) (1999), 15(6), 974-977).

Lin et al discloses throughout the article at e.g., the abstract:

> With the isocaudamers which have different recognition sequences and produce compatible cohesive ends, chimeric multi-epitope Plasmodium falciparum DNA vaccines including the multiplication of the single copy epitope and the tandem linkage of different kinds of epitopes were flexibly constructed. A specific B-cell response was detected by ELISA after the immunization of BALB/c mice with the chimeric antigen and demonstrated the usefulness of this strategy of constructing multi-epitope DNA vaccines.

Accordingly, the specific method steps of Lin using specific components anticipates or renders obvious the broad claimed method using broad components in the method.

Response to Arguments

Applicants recognize that Lin discloses the use of isocaudamers having different recognition sequences to produce chimeric multi-epitope Plasmodium falciparum DNA vaccines. But argue that there is no disclosure of randomly assembling polyepitope chimeric genes with different lengths from the nucleic acid molecules encoding randomly combined bi-epitopes as is required by step (c) of each independent claim. Further, Lin does not disclose isolating polyepitope chimeric genes into a plurality of different length ranges, purifying and amplifying the isolated polyepitope chimeric genes, subcloning the purified and amplified polyepitope chimeric genes into expression vectors, or transforming prokaryotic hosts with the expression vectors to obtain polyepitope chimeric gene expression libraries, the expression libraries corresponding to different length ranges into which the polyepitope chimeric gene libraries were isolated. Further, Lin does not disclose assessing the diversity of the polyepitope chimeric genes in the expression libraries, and selecting at least one polyepitope chimeric gene library based on diversity for use in preparing chimeric gene vaccines. In addition, Lin does not disclose immunizing

animals with the polyepitope gene expression libraries to provide expression products of the polyepitope chimeric genes. Nor does Lin disclose detecting the immunogenicity of the expression products of the polyepitope chimeric genes. Lin does not disclose selecting at least one polyepitope chimeric gene expression library based on the diversity of the polyepitope chimeric gene expression libraries and the immunogenicity of the expression products of the polyepitope chimeric genes in the polyepitope chimeric gene expression libraries. Finally, Lin does not disclose screen the selected at least one polyepitope chimeric gene expression library to identify polyepitope chimeric gene clones for use as polyepitope chimeric gene vaccines. Because Lin does not expressly or inherently disclose at least one step of the presently claimed method, Lin cannot and does anticipate that invention.

In reply, the different argued length would have been inherently taught by Lin's description of the different recognition sequences (i.e., of different length) or would have been obvious to determine. The disclosure of Lin of the tandem linkage reads on the bi-epitopic claim. Furthermore since the polyepitope of Lin elicits antibody responses hence, the argued immunogenicity of the product would be inherent to the prior art

teachings. [Please refer to the PCT search report which cites this reference as an anticipatory reference.] It would be within the ordinary skill in the art to isolate the different length ranges since as known in the art library produces a diverse (range) of compounds. [This is recognized no less by applicants at e.g., paragraph [0038] which states "…..five groups of randomly assembled polyepitope chimeric genes of respectively 300, 800, 1200, 2000 and 4000 bp are separated. **It is understood that one skilled in the art may set any desired length ranges**……."] (Emphasis added).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 2-3, 8-9 and 13-25, as amended and newly added, are rejected under 35 U.S.C. 103(a) as being unpatentable over Sette et al (USP 7026443) or Fikes (USP 6602510) in view Richards et al (USP 6291214) or applicants' admission of known prior art for reasons of record as repeated below.

Sette et al discloses throughout the patent at e.g., col. 5, line 65 up to col.6, line 11:

> ...Methods for monitoring or evaluating an immune response to HPV in a patient having a known HLA-type. Such methods comprise incubating a T lymphocyte sample from the patient with a peptide composition comprising an HPV epitope that

has an amino acid sequence described in Tables VII to Table XX which binds the product of at least one HLA allele present in the patient, and detecting for the presence of a T lymphocyte that binds to the peptide. A CTL peptide epitope may, for example, be used as a component of a tetrameric complex for this type of analysis……
An alternative modality for defining the peptide epitopes is to recite the physical properties, such as length……

Sette et al further discloses at e.g., col. 10, lines 10-22:

A "vaccine" is a composition that contains one or more peptides of the invention. There are numerous embodiments of vaccines in accordance with the invention, such as by a cocktail of one or more peptides; one or more epitopes of the invention comprised by a polyepitopic peptide; or nucleic acids that encode such peptides or polypeptides, e.g., a minigene that encodes a polyepitopic peptide. The "one or more peptides" can include any whole unit integer from 1-150.

Sette discloses in e.g., Example 10

This example illustrates the procedure for the selection of peptide epitopes for vaccine compositions of the invention. The peptides in the composition can be in the form of a nucleic acid sequence, either single or one or more sequences (i.e., minigene) that encodes peptide(s), or can be single and/or polyepitopic peptides.

The following principles are utilized when selecting an array of epitopes for inclusion in a vaccine composition. Each of the following principles is balanced in order to make the selection.

When creating polyepitopic compositions, e.g. a minigene, it is typically desirable to generate the smallest peptide possible that encompasses the epitopes of interest. The principles employed are similar, if not the same, as those employed when selecting a peptide comprising nested epitopes.

In cases where the sequences of multiple variants of the same target protein are available, potential peptide epitopes can also be selected on the basis of their conservancy. For example, a criterion for conservancy may define that the entire sequence of an HLA class I binding peptide or the entire 9-mer core of a class II binding peptide be conserved in a designated percentage of the sequences evaluated for a specific protein antigen. (Reads on claim 1, step d)

In Example 11 Sette discloses:

Construction of Minigene Multi-epitope DNA Plasmids

This example provides general guidance for the construction of a minigene expression plasmid. Minigene plasmids may, of course, contain various configurations of CTL and/or HTL epitopes or epitope analogs as described herein.
A minigene expression plasmid typically includes multiple CTL and HTL peptide epitopes. In the present example, HLA-A2, -A3, -B7 supermotif-bearing peptide epitopes and HLA-A1 and -A24 motif-bearing peptide epitopes are used in conjunction with DR supermotif-bearing epitopes and/or DR3 epitopes. HLA class I supermotif or motif-bearing peptide epitopes derived from multiple HPV antigens, preferably including both early and late phase antigens, are selected such that multiple supermotifs/motifs are represented to ensure broad population coverage. Similarly, HLA class II epitopes are selected from multiple HPV antigens to provide broad population coverage, i.e. both HLA DR-1-4-7 supermotif-bearing epitopes and HLA DR-3 motif-bearing epitopes are selected for inclusion in the minigene construct. The selected CTL and HTL epitopes are then incorporated into a minigene for expression in an expression vector.

This example illustrates the methods to be used for construction of a minigene-bearing expression plasmid. Other expression vectors that may be used for minigene compositions are available and known to those of skill in the art.

Overlapping oligonucleotides that can, for example, average about 70 nucleotides in length with 15 nucleotide overlaps, are synthesized and HPLC-purified. The oligonucleotides encode the selected peptide epitopes as well as appropriate linker nucleotides, Kozak sequence, and signal sequence. The final multiepitope minigene is assembled by extending the overlapping oligonucleotides in three sets of reactions using PCR…….

For example, a minigene can be prepared as follows. For a first PCR reaction, each of two oligonucleotides are annealed and extended: In an example using eight oligonucleotides, i.e., four pairs of primers, oligonucleotides 1+2, 3+4, 5+6, and 7+8 are combined…. The full-length dimer products are gel-purified, and two reactions containing the product of 1+2 and 3+4, and the product of 5+6 and 7+8 are mixed, annealed, and extended for 10 cycles. Half of the two reactions are then mixed, and 5 cycles of annealing and extension carried out before flanking primers are added to amplify the full length product. The full-length product is gel-purified and cloned into pCR-blunt and individual clones are screened by sequencing.

Fikes at e.g., throughout the patent at e.g., col. 30, line 35:

IV.J.1. Minigene Vaccines

A number of different approaches are available which allow simultaneous delivery of multiple epitopes. Nucleic acids encoding multiple epitopes are a useful embodiment of the invention; discrete peptide epitopes or polyepitopic peptides can be encoded. The epitopes to be included in a minigene are preferably selected according to the guidelines set forth in the previous section. Examples of amino acid sequences that can be included in a minigene include: HLA class I epitopes, HLA class II epitopes, a ubiquitination signal sequence, and/or a targeting sequence such as an endoplasmic reticulum (ER) signal sequence to facilitate movement of the resulting peptide into the endoplasmic reticulum.

…..A multi-epitope DNA plasmid encoding nine dominant HLA-A*0201- and A11-restricted CTL epitopes derived from the polymerase, envelope, and core proteins of HBV and human immunodeficiency virus (HIV), a PADRE.RTM. universal helper T cell (HTL) epitope and an endoplasmic reticulum-translocating signal sequence have been engineered. Immunization of HLA transgenic mice with this plasmid construct resulted in strong CTL induction responses against the nine CTL epitopes tested.

For example, to create a DNA sequence encoding the selected epitopes (minigene) for expression in human cells, the amino acid sequences of the epitopes may be reverse translated. A human codon usage table can be used to guide the codon choice for each amino acid. These epitope-encoding DNA sequences may be directly adjoined, so that when translated, a continuous polypeptide sequence is created. However, to optimize expression and/or immunogenicity, additional elements can be incorporated into the minigene design such as spacer amino acid residues between epitopes.

The minigene sequence may be converted to DNA by assembling oligonucleotides that encode the plus and minus strands of the minigene. Overlapping oligonucleotides (30-100 bases long) may be synthesized, phosphorylated, purified and annealed under appropriate conditions using well known techniques. The ends of the oligonucleotides can be joined, for example, using T4 DNA ligase. This synthetic minigene, encoding the epitope polypeptide, can then be cloned into a desired expression vector……

……Optimized peptide expression and immunogenicity can be achieved by certain modifications to a minigene construct……

Once an expression vector is selected, the minigene is cloned into the polylinker region downstream of the promoter. This plasmid is transformed into an appropriate bacterial strain, and DNA is prepared using standard techniques. The orientation and DNA sequence of the minigene, as well as all other elements included in the vector, are confirmed using restriction mapping and DNA

> sequence analysis. Bacterial cells harboring the correct plasmid can be stored as cell banks.
>
> Target cell sensitization can be used as a functional assay of the expression and HLA class I presentation of minigene-encoded epitopes. For example, the plasmid DNA is introduced into a mammalian cell line that is a suitable target for standard CTL chromium release assays. The transfection method used will be dependent on the final formulation, electroporation can be used for "naked" DNA, whereas cationic lipids allow direct in vitro transfection. A plasmid expressing green fluorescent protein (GFP) can be co-transfected to allow enrichment of transfected cells using fluorescence activated cell sorting (FACS). The transfected cells are then chromium-51 (.sup.51 Cr) labeled and used as targets for epitope-specific CTLs. Cytolysis of the target cells, detected by .sup.51 Cr release, indicates both the production and HLA presentation of, minigene-encoded CTL epitopes. Expression of HTL epitopes may be evaluated in an analogous manner using assays to assess HTL activity.
>
> In vivo immunogenicity is a second approach for functional testing of minigene DNA formulations. Transgenic mice expressing appropriate human HLA proteins are immunized with the DNA product…..Once again, lysis of target cells that were exposed to epitopes corresponding to those in the minigene, demonstrates DNA vaccine function and induction of CTLs. Immunogenicity of HTL epitopes is evaluated in transgenic mice in an analogous manner.

Each of Sette and Fikes does not teach isocaudamer linkage.

Richards discloses throughout the patent at e.g., col. 25, lines 7-25:

> Both within and external to the lacZ.alpha. gene we have incorporated restriction enzyme sites needed for compatibility with commercial cDNA library synthesis methods. These include methods for either partial or random fragments. Most of these will not have the translation-initiation sites needed for protein expression. Therefore, it is desirable to have an efficient translation start site

available on the cloning vector…….The restriction enzyme Esp3AI is an isocaudamer of EcoRI and so the pSK213 vector is compatible with EcoRI/XhoI-derived methods. This allows one to create one cDNA and clone it into the vector twice; once at the EcoRI site and including prokaryotic transcription, and a second time at the Esp3AI site and exclude transcription from occurring in E. coli.

Applicants at page 10, line 5-6 disclose:

….Various 5 isocaudamers are known in the art, which may be used in the method of the present invention.

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use isocaudamer linkage in the method of either Sette or Fikes for the advantage taught by Richards above. Because of this known advantage one would be motivated to use said linkage. One would have a reasonable expectation of success in obtaining a polyepitopic chimera gene vaccine since as applicants acknowledge said various linkage had been used and are known in the art in making polyepitopic chimeric gene vaccine. Nor does Lin render the presently claimed invention obvious. There is no teaching, suggestion or motivation in Lin to, inter alia, randomly assemble the nucleic acids molecules encoding bi-epitopes into polyepitope chimeric genes with different lengths, nor to isolate the polyepitope chimeric genes into a plurality of different length ranges, nor to clone the polyepitope

chimeric genes into expression vectors to obtain polyepitope chimeric gene expression libraries, nor to assess the diversity of those libraries. Thus, Lin would not render the presently claimed invention obvious to one or ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicants argue that Sette et al., who disclose polyepitope gene vaccines for HPV, actually teach away from the presently claimed invention by the method disclosed in their apparently prophetic Example 11 for constructing minigene multi-epitope DNA plasmids. Sette et al. disclose plasmids including multiple CTL and HTL peptide epitopes, such as HLA-A2 supermotif-bearing epitopes, HLA-A1 motif-bearing epitopes, HLA DR supermotif- bearing epitopes. Sette et al. advise including epitopes derived from multiple viral antigens, in order to ensure broad population coverage. However, Sette et al. are indifferent to the sequence in which the multiple epitopes are linked together in the minigene. Thus, one of ordinary skill in the art would, following the disclosure of Sette et al., construct polyepitope chimeric gene vaccines with no attempt to randomize the sequence of epitopes within the

construct, and without any recognition that the sequence could have an effect on the immunogenicity of the construct. Similarly, Fikes et al. disclose minigene vaccines incorporating multiple epitopes, but fail to disclose any recognition that the sequence of epitopes in the construct may have an effect on immunogenicity. Fikes et al. advise that optimized peptide expression and immunogenicity can be achieved by incorporating introns to facilitate efficient gene expression, and that expression can be increased mRNA stabilization sequences and sequences for replication in mammalian cells (co. 31, lines 35-42). However, Fikes et al. fail to disclose randomizing the sequence of epitopes in the construct and screening for optimized immunogenicity. Thus, the combination of references cited by the Examiner does not make out a prima facie case of obviousness.

In reply, applicants' arguments that Sette et al are indifferent to the sequence in which the multiple epitopes are linked together in the minigene are not commensurate in scope with the claims. The claims do not recite any sequences. Furthermore, applicants cannot attack the references individually when the rejection is based on the combination of references. The test for combining references is not what the

individual references themselves suggest but rather what the combination of the disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 CCPA 1971. The court must approach the issue of patentability in terms of what would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the **sum of all the relevant teachings in the art, not in view of the first one and then another of the isolated teachings in the art.** In re Kuderna, 165 USPQ 575 CCPA 1970. (Emphasis added).

Thus, while Sette does not teach e.g., the isocaudamer linkage, as argued however, Richards does. Richards teaches the advantages in the use of isocaudamer, which is a well-known linkage, as admitted by applicants. Because the linkage method is well known in the art and because of its advantages one having ordinary skill in the art would be motivated to modify the method of Sette or Fikes to arrive at the claim method.

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. WESSENDORF whose telephone number is (571)272-0812. The examiner can normally be reached on flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TERESA WESSENDORF/
Primary Examiner, Art Unit 1639